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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/386,709	08/31/99	BRAYDEN D	99.1081.US

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EXAMINER	
GRASER, J	
ART UNIT	PAPER NUMBER
1645	15

DATE MAILED: 08/15/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/386,709	Applicant(s) Brayden
	Examiner Graser, Jennifer	Art Unit 1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Request for CPA & Amendt. H (5/23/01)*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3, 5-9, and 11-20* is/are pending in the application.

4a) Of the above, claim(s) *1-3, 5-9, 11, and 12* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) ~~13-20~~ 21-37 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 7/23/01 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/386,709 is acceptable and a CPA has been established. An action on the CPA follows.

Claims 1-3, 5-9, 11 and 12 were previously withdrawn from consideration as being drawn to a non-elected invention. Claims 21-37 are currently under examination.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 21, 22 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andrianov et al. (US Patent No. 5,807,757).

Andrianov et al disclose a method for preparing polyphosphazene microspheres by coacervation (abstract). Andrianov et al disclose that the process of coacervation allows for the microspheres to be produced with a controlled microsphere size distribution without the use of elevated temperatures, organic solvents, water-insoluble core materials or complex manufacturing equipment, such as spray equipment and eliminates generation of the aerosol (column 2, lines 15-23 and lines 51-55). It is taught that the coacervation process is highly reproducible and

generates microspheres with an improved, more narrow microsphere size distribution compared to the spray technique and, contrary to the microspheres obtained by spray method, coacervation microspheres do not contain significant amount of larger size aggregates or amorphous precipitate (column 2, lines 55-60). It is specifically taught that this important for the preparation of microspheres for vaccine delivery since the uptakes of these microspheres by M cells is limited to the particles having a diameter of 10um or less (column 2, lines 61-65). It is disclosed that biological material can be encapsulated by mixing the material with either polyphosphazene solution before microsphere preparation, or with prepared polyphosphazene microspheres (col. 2, lines 24-29). Andrianov et al teach that the phosphazene polyelectrolyte is preferably *biodegradable* to prevent eventual deposition and accumulation of polymer molecules at distant sites in the body, such as the spleen (column 4, lines 32-40). The paragraph bridging columns 5 and 6, disclose that the microspheres formed by coacervation, may be employed as carriers of a biological material such as an antigen, which is capable of eliciting an immune response in an animal. The antigen may be derived from a cell, bacterium, virus particle or a portion thereof and may be a protein, peptide, polysaccharide, glycoprotein, glycolipid, nucleic acid, or combination thereof which elicits an immune response in an animal, including mammals, birds and fish (column 6,lines 1-10). It is taught that the microspheres which contain antigen may be administered as a vaccine by any method known to those skilled in the art that elicits an immune response, including parenterally, orally or by transmembrane or transmucosal administration (column 6, lines 30-40). The use of pharmaceutically acceptable carrier with the microspheres, i.e., PBS, is taught.

Although Andrianov et al do not specifically recite that the at least 50% of the microparticles are less than 5um (less than 3um or less than 600nm), they do teach that any particle size may be made and they specifically teach the importance of microparticles of less than 10um for use as vaccines. It is taught that coacervation enables one to recover an increased yield of microspheres having a size in the micron range (up to 90 differential percent by volume and 95 differential percent by number), and produce microspheres of other sizes if needed without the use of elaborate equipment (column 5, lines 55-61). Example 9 teaches that 90% of particles by number and size are smaller than 6.6um, Example 6 teaches that microparticles with a mean size between 4-6um were formed and Example 2 teaches that the percentage of microspheres under 10um is 90%(by volume) and 99.7% (by number). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce microspheres by the method taught by Andrianov et al in the size ranges recited in the instant claims because the prior art literature, as cited by Andrianov and cited in the previous Office Actions, is consistent with suggesting a size of less than 10um, preferably less than 5um for uptake of the Peyer's patches to occur. It was known in the prior art that conflicting reports have appeared concerning the optimal size for vaccine delivery, yet the art is consistent in suggesting sizes of less than 10um and approximately 500nm which is the ideal size for phagocytosis by antigen presenting cells.

4. Claims 24-28, 30-34 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andrianov et al. (US Patent No. 5,807,757) in view of Jones (Infect. Immun., 1996, 64(2): 489-494) and Shahin et al (Infect. Immun., 1995, 63(4): 1195-1200).

The teachings of Andrianov et al are set forth above. However, they do not specifically recite that at least one of the antigens to be encapsulated is a *B.pertussis* antigen, including inactivated pertussis toxin (Ptd), filamentous hemaglutinin (FHA) and pertactin or that two subpopulations of microparticles comprising a different antigen entrapped or encapsulated by the biocompatible, biodegradable polymer may be used.

Jones et al teach that fimbriae from *Bordetella pertussis* encapsulated in poly(lactide-co-glycolide) microparticles of a size appropriate for uptake by the immune inductive tissues of the gastrointestinal tract could protect mice from *B.pertussis* respiratory infection upon oral administration (abstract). It is disclosed that the mean diameter of the microparticles was 2.04um, with 90% of microparticles having diameters within the narrow range of 0.8 to 5.3 um (see page 490, Results section). The microparticles were prepared through a solvent extraction technique (top of page 490, column 1). It is further disclosed that analysis of the mechanism of particle uptake by M cells in mouse gut has clearly shown that this is restricted to materials with diameters less than or equal to 10um (page 492, column 2). It is further disclosed that smaller microparticles (1- to 10- um) were more immunogenic than larger particles (20- to 50- um), as the smaller microparticles were rapidly phagocytosed and distributed (page 290, column 1).

Shanin et al disclose that purified *Bordetella pertussis* antigens, encapsulated in biodegradable poly (DL-lactide-cp-glycolide) (DL-PLG) microspheres are effective vaccines. The reference discloses that microencapsulated pertussis toxoid, filamentous hemagglutinin, and pertactin all retained their immunogenicity when administered parenterally (abstract). It is also

disclosed that intranasal administration of these microencapsulated antigens elicited high levels of specific antibody coinciding with protection against infection when these microspheres are administered to the respiratory tract (abstract).

Shanin and Jones and teach microparticles comprising antigens from *B.pertussis*. Andrianov specifically teaches the use of bacterial antigens in their microspheres. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate one, or all, of the *B.pertussis* antigens taught by Shanin and Jones into the microspheres taught by Andrianov et al since these antigens were well known in the prior art at the time the invention was made and were shown to be good vaccine components. Jones specifically teaches the use of smaller microparticles allows for a more rapid phagocytosis and distribution. Further, it would have been obvious that both Ptd and filamentous hemagglutinin could be encapsulated together because the person of ordinary skill in the art would expect such a mixture to improve the range of immune response in an additive or cumulative manner. Multi-component vaccines were well known in the art at the time the invention was made and the addition of more than one *B.pertussis* antigen in the microparticles, particularly when these antigens have already proven to be effective vaccine components individually, would have been obvious.

5. Claims 23, 29, 35 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andrianov et al. (US Patent No. 5,807,757) in view of Singh et al (Adv. Drug Delivery Reviews, 1998, 34: 285-304).

The teachings of Andrianov et al are set forth above. However, they do not particularly exemplify the use of a polymer comprising lactic acid, or an enatiomer of lactic acid with glycolic acid or an enantiomer or glycolic acid in their microspheres.

Singh et al teach methods of preparation and characterization of polymeric antigen delivery systems for oral administration. Singh et al. disclose that a number of different polymers have been evaluated for the development of oral vaccines including naturally occurring biodegradable polymers, such as starch, alginates, and biodegradable polymers, such as polylactide-co-glycolides (PLG) (page 286, column 2). It is disclosed that PLG are biodegradable polymers with a long history of safe use in humans (page 287, column 2). The reference teaches that for oral antigen delivery with PLG microparticles, the desired size range is usually less than 5 um (page 288, column 2). Page 291, column 2, teaches that greater than 90% of the PLG microparticles have a mean size of less than 5 um. Polyamino acid microspheres are taught which have size ranges ranging from 0.1 to 5 um.

It would have been prima facie obvious to one of ordinary skill in the art to substitute the PLG polymers taught by Singh in the coacervation methods taught by Andrianov et al because Singh et al teaches that PLG are biodegradable polymers with a long history of safe use in humans and Andrianov specifically teach that coacervation methods have many advantages over solvent evaporation methods, such as highly reproducible and generates microspheres with an improved, more narrow microsphere size distribution compared to the spray technique and, contrary to the microspheres obtained by spray method, coacervation microspheres do not contain significant

amount of larger size aggregates or amorphous precipitate (column 2, lines 55-60). Absent evidence to the contrary, one of ordinary skill in the art would expect another biodegradable polymer, such as PLG, to work equally as well in the coacervation methods taught by Andrianov et al. and would allow for the production of a safe and effective microparticle vaccine.

6. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 308-4242 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 308-1742. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Jennifer Graser 8/13/01

Jennifer Graser
Primary Examiner
Art Unit 1645